DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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Warning Letter

VIA FEDEX

WL: 320-01-07

JAN 1 1 2001

Dr. Mikael Blomqvist
Strängnäs Plant Director
Pharmacia Corporation
Mariefredsvägen 37
S-645 41 Strängnäs, Sweden

Dear Dr. Blomqvist:

We have completed our review of the inspection of your Strängnäs active pharmaceutical ingredient (API) manufacturing operations, which includes Swedish sites in Strängnäs, Brunna, and Stockholm, by Investigator Thomas J. Arista and Chemist Robert D. Tollefsen during the period of June 13-22, 2000. The inspection revealed significant deviations from U.S. current good manufacturing practices (CGMP) in the manufacture of bulk Somatropin and Dalteparin Sodium used for parenteral products. The deviations were presented to you on an Inspectional Observations (FDA-483) form, at the close of the inspection. These CGMP deviations cause your API's to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

Specific areas of concern include, but are not limited to:

1. The Strängnäs API manufacturing operation uses both the [ ]System) and [ ]network computer software programs for materials and data management functions. The [ ]performs functions typical of a laboratory information management system. The quality control unit uses this program for disposition of materials, special studies, stability testing programs, and generation of summary test reports. Once material is dispositioned, [ ] communicates information to the [ ]network program used by warehouse and production personnel to control material in storage and production. Both the [ ] and [ ]network programs work in concert acting as the sole source of

information which controls and maintains the status of raw materials and finished goods in the warehouse. Your operations use these programs in a similar manner to control in-process materials during manufacturing operations. These network program systems are deficient in that:

a. The [ ] network program lacked adequate validation and/or documentation controls. For example:
   - The system design documentation has not been maintained or updated throughout the life of the [ ] software dating back to 1985 despite significant changes and modification that have taken place. These include program code, functional/structural design, diagrams, specifications, and text description of other programs that interface with [ ]
   - The program was not controlled by revision numbers to discriminate one revision from the other.
   - Inadequate standard operating procedures to ensure that records are included with validation documentation, maintained and updated when changes were made.
   - Significant deficiencies regarding documentation controls were reported. Documents were either not dated, lacked a documentation control number, were missing, were reported in pencil on uncontrolled pages, or dates were crossed out without initials, dates, or explanation.
   - There was no assurance that complete functional testing had been preformed in the [ ] system. For example you failed to assess all historical testing and compare it with current functionality to ensure that all current functionality has been adequately evaluated.

b. The [ ] network program lacked adequate validation and/or documentation controls. For example:
   - The program uses a purchased custom configurable materials management software package. The software validation documentation failed to adequately define, update and control significant elements customized to configure the system for the specific needs of the operations. The following had not been maintained or updated from original release/design specification dating back to approximately 1985:
     - Revision control system.
     - Validation records did not address the order of libraries which effect function.
     - Structural and functional diagrams and design descriptions.
     - Complete diagrams with text description identifying other network programs which interface with [ ]
   - Deficiencies regarding documentation controls such as maintenance of records, lack of review and approval of change control and other similar records.
   - Inadequate standard operating procedures to ensure that records are included with validation documentation, maintained and updated when changes are

made.

c. The wide area network also identified as the[ ]is used to connect network applications to local area networks[ ]at Strängäs API operational facilities. The[ ]and[ ]run both the[ ]and[ ] network application at each site by departments using these programs to perform their GMP function. Both the[ ]and[ ]documentation were not included in the[ ]and[ ]validation efforts and therefore lacked adequate documentation controls.

Your response for the[ ]acknowledges that the system has not been maintained throughout its life and there are gaps in the documentation. You indicate rather than expending resources on reviewing validation documentation that in some cases is 15 years old, you are looking forward to a replacement of the[ ]system with a new validated computer system in the near future. In the interim your validation effort was to review only the current system documentation with respect to the Investigator's computer concerns. You evaluated the functionality and reliability of[ ]by comparing the printout of 21 US batches against source documents and no errors were found. As a result you concluded that the[ ]system functions correctly and reliably and has been validated. Your response fails to trace back to source code, and the related software development cycle which establish evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. Software is validated in its controlled development and in control of ongoing maintenance of the software and its documentation throughout its life cycle. You make no commitment to retrospectively put the historical documentation together.

Your response for[ ]indicates upgrading[ ]version[ ]installed during 1997 to version[ ]on or about December 2001 and inclusion of corrective actions in version[ ]Also you will continue to use, and complete a retrospective evaluation of [ ]on or about December 2000. The inspection reports that the documents reviewed did not define the system as being validated but was a qualification document for the[ ]version upgrade. The records did not describe the custom configuration of the[ ]system as it is in place. Your response did not evaluate requirements or trace changes to determine side effects. Further, your response failed to address the issue of what sites are approved to use the[ ]application nor does it address defining what restrictions will be in place for each site with respect to defining what functions in[ ]are approved for use at each site. In order to consider a computer system to be validated, all elements which make up the system must be clearly defined. Appropriate systems definition documentation, properly updated when necessary throughout the life cycle of the software, is part of the control and ongoing maintenance of a computer program. Your response fails to discuss extending the retrospective evaluation to other elements of the system needing to be defined and controlled as part of the overall configuration management.

It could be difficult to retrospectively validate a computer system if there were changes and revisions that were not documented and the cumulative affects of many revisions had not been assessed. Lack of sufficient system documentation would make it impossible to perform meaningful retrospective validation. FDA concludes that the [ ] and [ ] systems lack adequate validation and therefore are unacceptable for use in the production of drug products. Please indicate whether you can perform a retrospective validation of the [ ] and [ ] systems or rely in the interim on manual operations, which use source documentation until the new validated computer systems are functional.

2. The Strängnäs local API production computer systems used in manufacturing operations, environmental control alarms and deviation tracking system lacked adequate validation and/or documentation controls. For example:

   a. The [ ] computer control system used to monitor and control manufacturing equipment and processes for API manufacturing operations lacked the following:
      - Assurance that system definition design documentation was up-dated to reflect changes that had taken place in the system.
      - Validation records did not address wiring diagrams.
      - Various documentation control deficiencies were reported such as identification and maintenance of validation records.

   b. The [ ] computer control system used to control the manufacturing process equipment during the [ ] at the Stockholm facility for Strangnas API operations, lacked the following:
      - Appropriate documentation procedures for handling historical application files.
      - Handling records generated with inaccurate time frames dating back ten years due to Y2K compliance related issues.

   c. The [ ] computer system used to monitor and control manufacturing equipment and processes in the manufacture of an API for [ ] and [ ] steps lacked the following:
      - Updating system definition documentation to reflect changes that had been performed on system.
      - Appropriate controls to ensure that only authorized personnel had access to the system.
      - Documentation of review/ approval, and controls for adequate maintenance of records.
      - Diagrams related to process flow, system layout, plumbing & installation (P&I), and wiring were not part of the validation documentation.

d. The [ ] Computer system that is accessed by personnel from various departments to include manufacturing, testing laboratory and Quality Assurance lacked the following:
   - Audit trail function of the database, to ensure against possible deletion and lost of records.
   - Absence of documentation defining the database, operating system, location of files, and security access to database.

e. The [ ] alarm system that communicates, records, and controls alarms such as air balance and temperatures for production, warehouse and testing areas lacked the following:
   - Documentation regarding functionality design and layout diagrams were found obsolete.
   - Validation documentation did not address signal lines between detection devices and computer.
   - Various documentation control deficiencies were reported such as review, approval, and maintenance of records.

3. Inadequate oversight by the Quality Control Unit (QCU) to ensure that controls which impact API quality are implemented for manufacturing operations. For example:

   a. The QCU failed to ensure that adequate procedures were put into place to define and control computerized production operations, failure investigations, equipment qualifications, and laboratory operations.

   b. The inspection reported numerous deficiencies regarding the lack of procedures, failure to follow procedures, and inadequate laboratory controls for documentation, storage and handling of samples pertaining to the stability and environmental monitoring programs.

4. Non-penicillin APIs with a reasonable possibility of penicillin contamination were not tested for the presence of penicillin prior to release for distribution. You have failed to demonstrate the absence of penicillin residues in your facility generated from the adjacent penicillin bulk powder manufacturing plant, and also the cafeteria that is shared by both facility employees. For example:

   a. There was no routine monitoring program for traces of penicillin from the adjacent facility or the cafeteria used by both manufacturing facilities.

   b. Your May 1994 evaluation of this situation was inadequate in that it failed to include test results of samples obtained from:
      - Your employees that were using the common cafeteria.
      - Various contact surfaces of your manufacturing facility such as doors handles, walls, floors, and work surfaces.

- Surface areas from [ ] floor master air intake units located on the adjacent side of the penicillin manufacturing facility.

c. Air handling systems. There were individual floor master air duct units which supply air to various production and office areas that either lacked schematics, or the schematics represented inaccurate information such as incorrect exhaust air filters. Furthermore, there was no verification and written procedures to ensure correct usage by contract personnel of [ ] filters required in the air filtration system which supplies air to various production areas.

Your response indicates an October/November 1998 and March/April 2000 monitoring period to evaluate the concentration of penicillin in outdoor air. The March/April 2000 monitoring found higher than expected levels of penicillin [ ] This information was not provided to the inspectors, and continues to lack test results from samples obtained from employees returning from the common-use canteen and surface samples from your facility. We also note that you are currently testing your non-penicillin product lots and monitoring the facility environment for traces of penicillin. However, your response does not discuss the adequacy of your sampling criteria, the test methodology requirements and future monitoring program. We wish to meet with you to discuss these issues.

Regarding the air handling system's schematics. The inspection noticed air units that draw air from the direction of the adjacent penicillin API manufacturer. There could be a concern for alarm in that these units provide air that may have some airborne contaminates which could include penicillin. Schematics which are either missing or incorrect would hamper adequate investigation of cross contamination and development of an adequate monitoring program.

5. Inadequate maintenance of equipment and utilities. For example:

a. There was no procedures or documentation of the [ ] water system checks for conductivity, temperature and leaks.
b. There was no documentary evidence showing a secondary review by firm officials of contractor's work to ensure that the orbital welds of the water system met specifications.
c. Procedures were not followed for handling miscellaneous manufacturing equipment, and used materials. Numerous stainless steel spare parts, a transfer hose, and a used pre-filter lacked records documenting their cleaning/usage status.
d. A pipe and two hoses, connected to [ ] distillation units, were in or on the waste line floor drains and lacked air breaks to prevent back-siphonage of water back to the [ ] distillation units.

Our review also included your company's response letters to the FDA-483 observations dated July 20, 2000, September 4 and 29, 2000, October 17, 2000, November 17 and 30,

2000. We acknowledge that many corrections have been made, or are in progress. Your response to observation 1 addressing the[ ]and[ ]computer validation and observation 4 addressing penicillin testing and monitoring issues were inadequate as discussed above. Except for observations 1 and 4, the corrections when fully implemented appear to satisfactorily address the deficiencies listed on the FDA-483.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

Please respond to this letter within 30 days of receipt. Your response should include copies of procedures generated as well as data collected in your correction to the deficiencies cited. Please identify your response with CFN 9610470. Until FDA can confirm compliance with CGMP's and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturere of active pharmaceutical ingredients.

Please contact Edwin Melendez, Compliance Officer, at the address and telephone numbers shown above, if you have any questions, written response or concerns regarding these decisions.

To schedule a reinspection of your facility after corrections have been completed, and your firm is in compliance with CGMP requirements, send your request to: Director, International and Technical Operations Branch, HFC-134, Division of Field Investigations, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 443-1855 or by fax at (301) 443-6919.

Sincerely,

/ for

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality

CC: Gary Harbour, Ph.D
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